# Regenerez® Degradation and Release Kinetics White Paper

secant group

PARTNERS FROM INSPIRATION TO REALIZATION

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## Introduction

Implantable biomaterials play a critical role in medical applications such as, cell therapy, regenerative medicine, tissue replacement, and biomedical devices. Of particular interest is the use of biomaterials in drug delivery systems. Implantable devices for sustained drug release offer advantages in patient compliance because the treatment regime can be less taxing than pills or injections. Some areas of application include pain management, contraception, diabetes maintenance, HIV treatment and prevention, as well as targeted controlled delivery for neurology, cardiology, ophthalmology, and oncology.

Long-acting implantables can improve the effectiveness of drug delivery by reducing side effects because local delivery may require a lower dose strength. Some other benefits of this route of administration include:

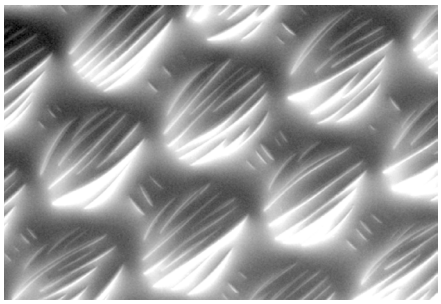
- Targeted delivery to a local surgical site
- Systemic delivery into the circulatory system
- Eliminates first pass metabolism of drug
- Sustained drug release within the therapeutic window over longer duration
- Tailored release of one or more drugs from a single implant
- Removal of the implant (and drug) if required due to an adverse reaction
- Possible shorter regulatory pathway through the 505(b)(2) approval pathway

Regenerez®, poly(glycerol sebacate) (PGS), is a biodegadable polymer with unique degradation properties that can be controlled by modulating its physical and chemical properties. Regenerez as a carrier for drug delivery can provide new therapeutic options and give formulators a wide range of design flexibility.

## Regenerez®

Regenerez is a bioresorbable elastomer synthesized by the polycondensation reaction between two naturally occurring metabolites, glycerol and sebacic acid. PGS has garnered much attention in the field of tissue engineering and regenerative medicine due to its elastomeric behavior, favorable mechanobiological properties and surface-erosion degradation in vivo.

In addition, the thermal and solubility properties of PGS make it easily formable into various constructs. These characteristics allow it to be cast neat into films using molds, or solvated and applied as a coating to different textile substrates (PGA, PET, PEEK, Nitinol). Technology has also been developed around the cold extrusion of PGS into different sized sheets, rods, and tubes.



PGS Coated PET

PGS Cast Film

Extruded PGS Tube

## Regenerez for Implantable Medical Devices

A majority of bioresorbable implants are comprised of PGA or PLGA. Unlike PGS, these polymers are bulk eroders, which lose a significant percentage of their mass, as well as mechanical integrity, at a specific time. Furthermore, these materials exhibit bolus release kinetics resulting in a slow release followed by a burst of the loaded drug. Surface eroders like PGS lose mass and mechanical strength at a linear rate over time. This degradation mechanism, which occurs via hydrolysis, makes PGS an ideal candidate for implantable drug delivery because it allows for localized, controlled release.

Additionally, the tunability of PGS makes it a desirable choice for polymeric drug delivery because the degradation (which is highly correlated with release rate) can be matched to fit the desired therapeutic profile. By adjusting the cure time or changing the initial reactant stoichiometry, PGS can display a wide range of degradation or release rates across a variety of active pharmaceutical ingredients (APIs). Surface erosion enables the amount of drug released per day to be tuned simply by altering the initial drug loading and PGS construct thickness, whether it's a cast film, coating, or extruded construct.

## Regenerez Demonstrates Surface Erosion In Vitro

In vitro degradation studies on PGS-coated PET knit mesh show that PGS behaves as a surface eroder. After an initial bolus release due to the fast degradation of low $M_w$ fractions, both a loaded and unloaded PGS coating degrade by surface erosion. Figure 1 illustrates the linear relationship between mass loss and degradation time. Studies have noted the discrepancy between in vitro and in vivo degradation rates of PGS[1,2], however surface erosion degradation is still observed in vivo due to its low permeability[3,4,5].

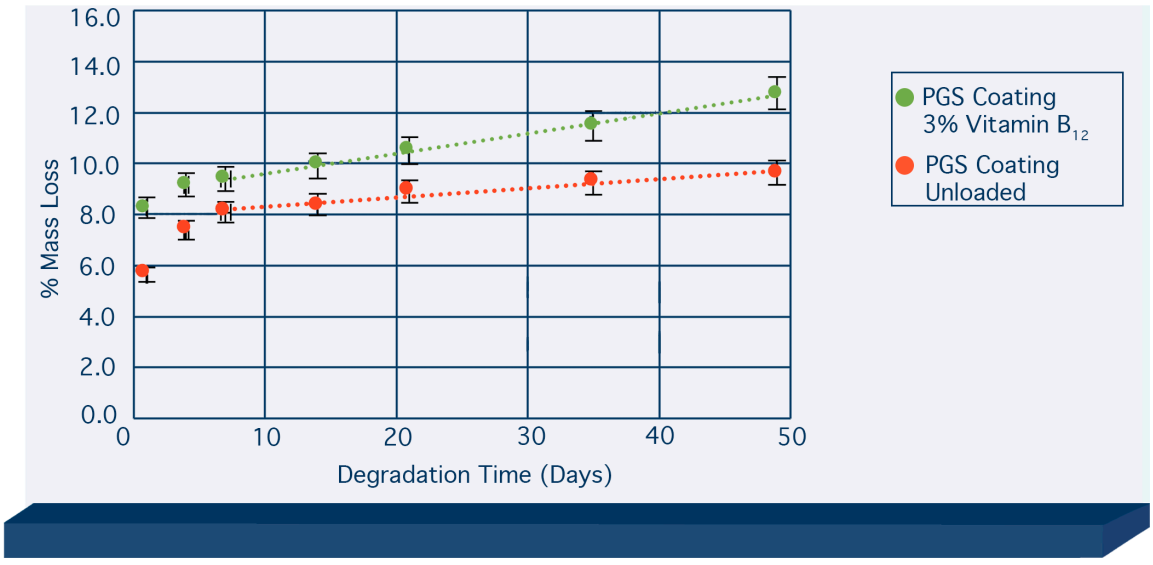



**Figure 1:** In vitro degradation results of loaded and unloaded PGS coatings conducted in 0.1M PBS at pH=7.4 and 37.0°C.

For a comparison to commonly used biosresorbables, the same study was conducted on a coating of PLGA 50:50 (ester terminated), a known bulk eroder. In vitro degradation behavior displayed classic bulk erosion in which little to no change is observed prior to an abrupt mass loss as shown in Figure 2.

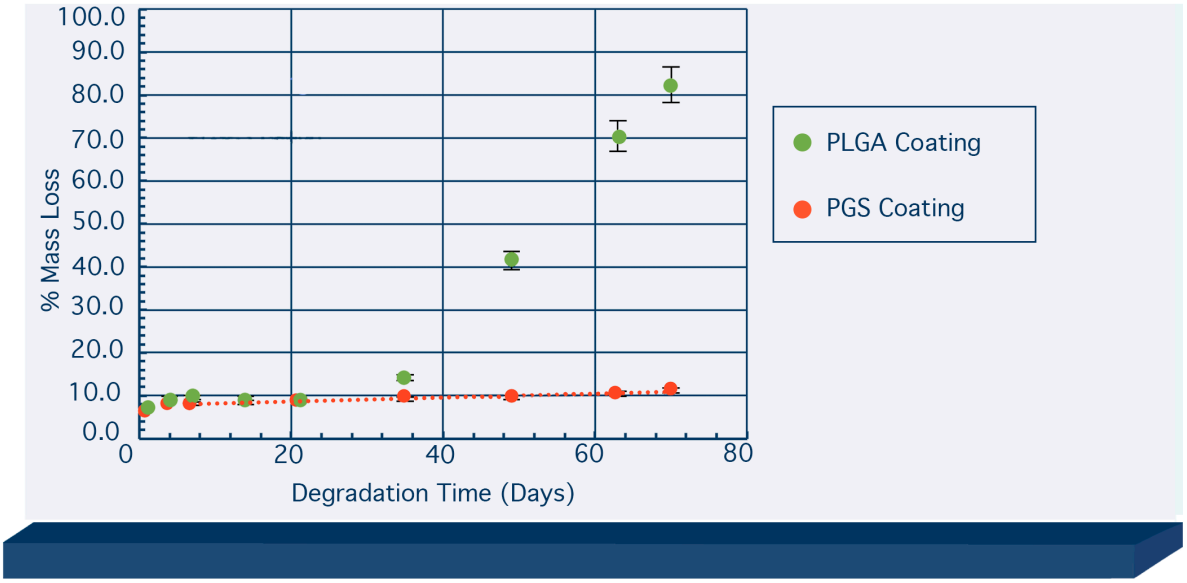



**Figure 2:** In vitro degradation results of PLGA 50:50 vs. PGS coatings conducted in 0.1M PBS at pH=7.4 and 37.0°C.

The effects of bulk degradation are also observed in the polymer morphology shown by SEM analysis of the degraded coatings (Figure 3). At Day 35 the PLGA film is intact but at Day 49 there is significant pitting in the film which corresponds to the observed mass loss. In contrast, the PGS coating maintains a controlled loss of coating thickness with no observable changes in morphology.

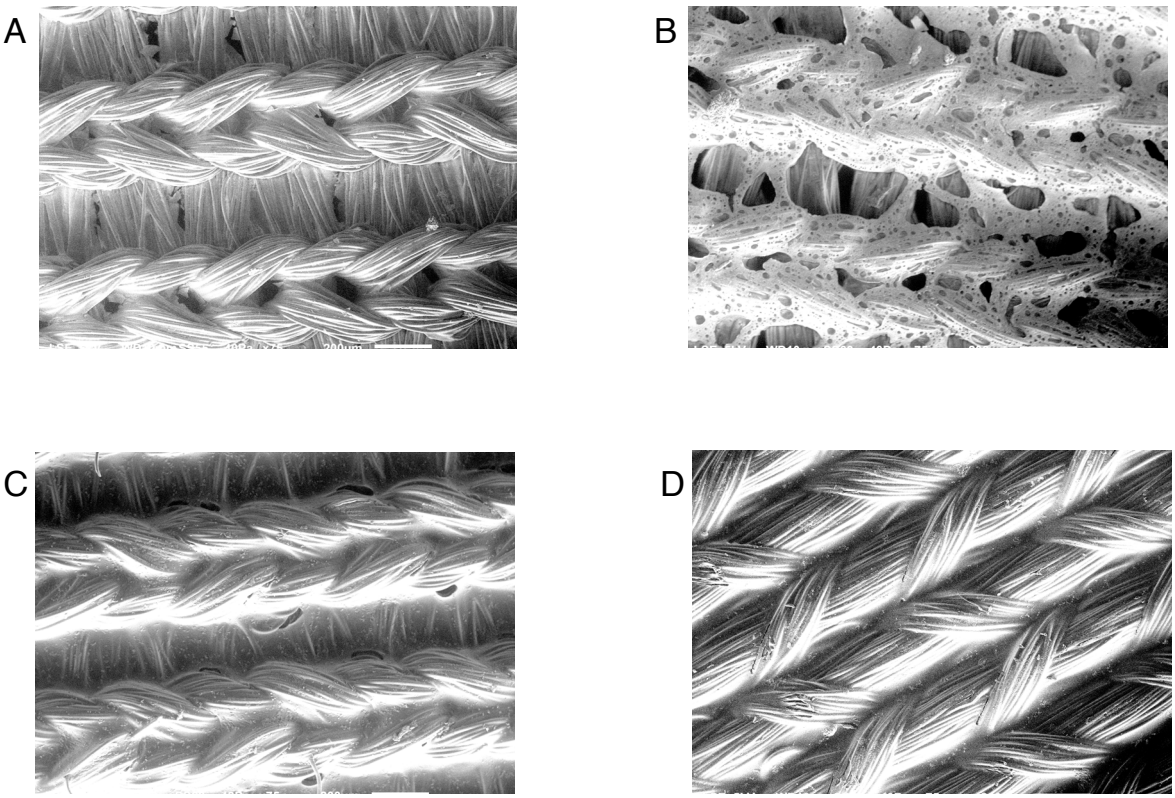



**Figure 3:** SEM images of PLGA coating after A) 35 days degradation and B) 49 days degradation and PGS coating after C) 35 days degradation and D) 49 days degradation

## Tunability of Regenerez Degradation Rate

The properties of the final PGS thermoset are controlled mostly by cure time, which determines the crosslink density of the resultant structure. Irrespective of form, whether a coating, film, or extruded construct, the crosslink density can be tuned by increasing or decreasing cure time. By increasing the cure time, the crosslink density increases therefore making it less susceptible to hydrolysis. This was demonstrated by curing PGS cast films for 48 and 96 hours. Mass loss analysis in Figure 4 shows that both samples degraded at a linear rate over time, with 48-hour cured samples degrading at a faster rate than 96-hour cured samples.

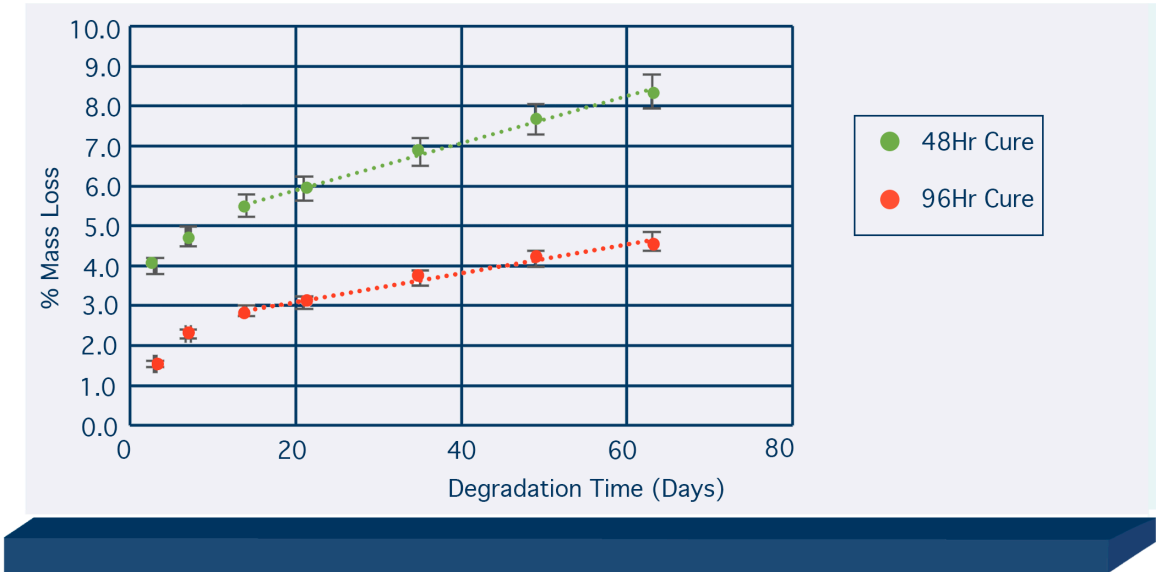



**Figure 4:** In vitro degradation results on effect of cure time on degradation rate of PGS cast films conducted in 0.1M PBS at pH=7.4 and 37.0°C.

Apart from cure time, the degradation rate of PGS can also be tuned by varying the stoichiometry of the reactants. Regenerez is typically manufactured using a 1:1 ratio of glycerol to sebacic acid. By adding more glycerol initially, the resultant thermoset polymer is less crosslinked and more hydophilic, therefore making the polymer more susceptible to hydrolysis. Adding more sebacic acid to the reaction has the reverse effect, causing the thermoset polymer to be more hydrophobic in character and therefore less susceptible to hydrolysis, as demonstrated in Figure 5.

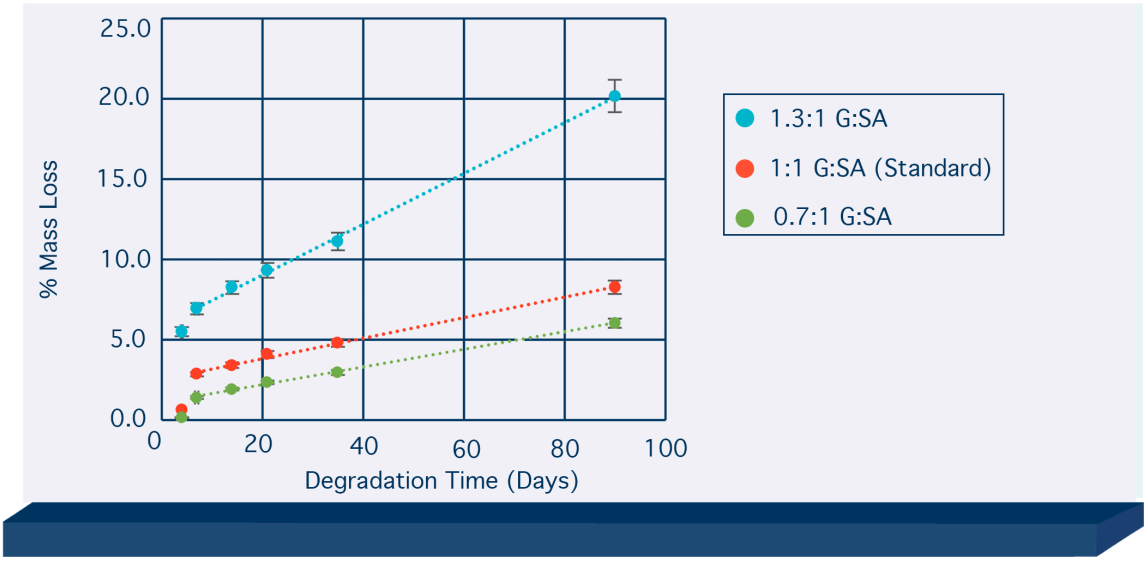



**Figure 5:** In vitro degradation results on effect of effect of stoichiometry on degradation rate of PGS cast films conducted in 0.1M PBS at pH=7.4 and 37.0°C.

## Surface Erosion of Regenerez Allows for Controlled Release of APIs

Mass loss values for cast films and coatings, both loaded with drug and unloaded, have demonstrated the surface erosion degradation mechanism of PGS in vitro. When drug-loaded, assuming homogenous distribution of the drug within the matrix, PGS should release the API at a controlled rate. To demonstrate this, Vitamin $B_{12}$ and curcumin were loaded into separate PGS coatings and drug release rate was monitored in vitro. From the graph depicted in Figure 6, the release rate of each drug over time remained linear after a minimal initial bolus release. This also demonstrates the capability of PGS to be combined with both water-soluble and water-insoluble drugs. As noted in the analysis of the mass loss data, release kinetics will be faster in vivo than in vitro, due to the additional effects of enzymatic and oxidative degradation in vivo.

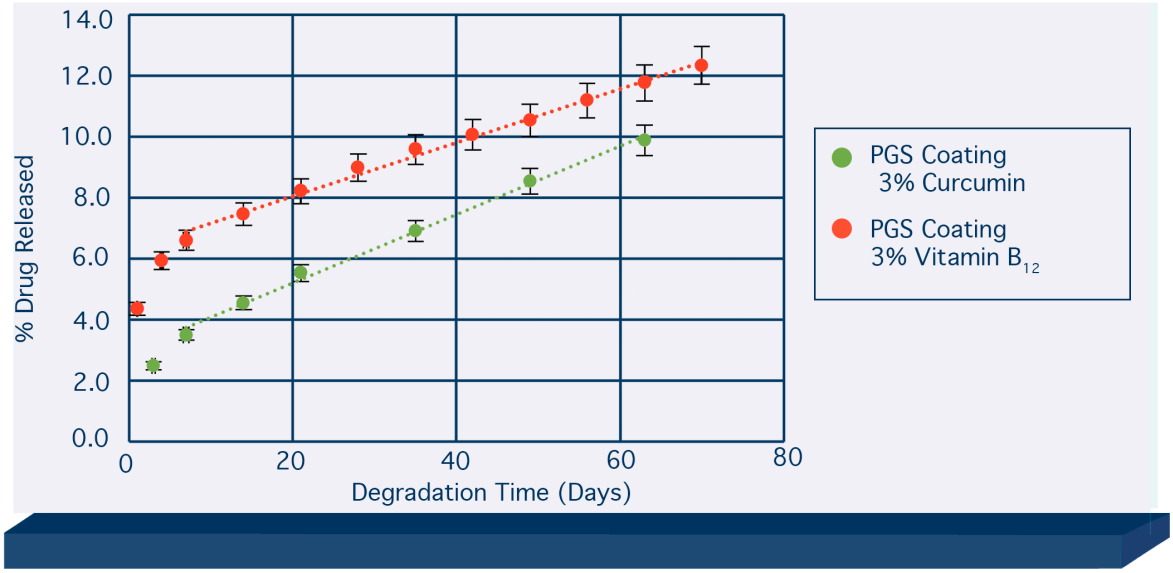



**Figure 6:** In vitro release rates for Vitamin $B_{12}$ and curcumin loaded PGS coatings conducted in 0.1M PBS at pH=7.4 and 37.0°C.

In a similar manner to unloaded PGS constructs, those containing API can be tuned by adjusting cure time, stoichiometry, film thickness, and % loading. In Figure 7, the effect of % drug loading on the amount of Vitamin $B_{12}$ released per day is demonstrated. Since PGS is a surface eroder, the amount of drug loading directly impacts the amount of drug released per day, but the overall proportion of drug released relative to initial loading amount remains the same across loading levels.

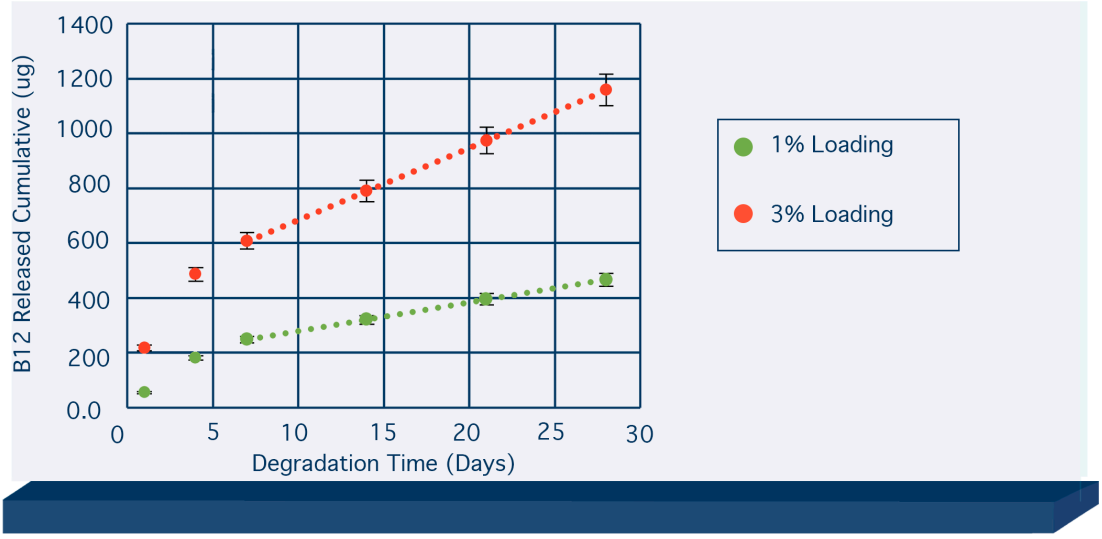



**Figure 7:** In vitro release of Vitamin $B_{12}$ from PGS cast films at different loading levels conducted in 0.1M PBS at pH=7.4 and 37.0°C.

## Conclusion

Controlled release is an attractive option to enhance the efficacy of an existing drug product or provide additional patient benefits in conjunction with an implantable device.

Drug-loaded Regenerez demonstrates minimal burst release followed by zero order kinetics that is agnostic to drug loading and drug solubility. This type of release behavior has the ability to overcome some major limitations that commonly used biodegradable materials have. Taken in combination with its tunable and surface eroding degradation properties, PGS offers a broadly customizable solution for polymeric drug delivery. Due to its elastomeric properties and ability to be formulated into various forms, PGS can be used for drug delivery by various routes of administration such as; intramuscular, intravaginal, subcutaneous, and Intraocular.

Although degradation and release rates have shown to be slower in vitro than in vivo, general trends between cure time, stoichiometry, and other tunable factors will still be observed.

## References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